REMARKS

Applicants respectfully request entry of the foregoing and continued examination of the subject matter identified in caption, as amended, pursuant to and consistent with 37 C.F.R. § 1.114 and in light of the following remarks.

Rejection Under 35 U.S.C. § 103(a)

Claims 32, 36, 38, 53 and 54 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (*Journal of Virology*. 1993; 67 (1): 3 15-322), Borysiewicz et al. (*Lancet*. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3:187-193), and Meyer et al. (*Journal of General Virology*. 1991; 72: 103 1- 103 8), as further evidenced by Boursnell et al. (US 5,719,054). Applicants traverse.

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. §2142. Applicants respectfully submit that these criteria have not been met in the present Office Action.

The cited references, alone or in combination, fail to recite all of the elements of the presently claimed invention or to provide an expectation of success or motivation to arrive at the claimed invention.

Lowy et al.

Lowy *et al.* rely on the use of recombinantly produced L1, L2 and E7 papillomavirus polypeptides assembled in VLPs. To this end, Applicants emphasize that VLPs mimic infectious virions in structure and morphology. Chimeric VLPs are composed of self assembled L1 polypeptides and a fusion product between L2 and E7 papillomavirus polypeptides. The incorporation of the E7 polypeptide into the L2 polypeptide allows the early epitopes at the surface of the VLP to be amenable to the immune effector cells. The chimeric VLPs elicit neutralizing antibodies that recognize the VLP-exposed E7 polypeptide.

However, aside from detecting neutralizing anti-E7 antibodies in immunized animals, Lowy *et al.* fail to demonstrate any therapeutic protection against HPV-induced tumors following administration of the chimeric VLP particles presenting E7 at their surface. It is known that production of antibodies involves humoral immunity and that efficient antitumoral responses require cell-mediated immunity. Several lines of evidence support the importance of the cell-mediated immune response to HPV antigens to prevent progression in HPV-associated dysplasia and cancers. To this end, Lowy *et al.* fail to disclose that the E7-presenting VLPs are able to protect against already existing papilloma-induced tumors.

The secondary references, combined with the primary reference, fail to remedy the deficiencies of Lowy et al. as discussed above.

Meyer et al.

Meyer *et al.* is merely a document providing background and summary information regarding the MVA virus.

Hagensee et al.

Hagensee *et al.* disclose the use of L1 and L2 papillomavirus genes for prophylactic purposes.

Borysiewicz et al. and Boursnell et al.

Borysiewicz *et al.* and Boursnell *et al.* both disclose the use of E6 and E7 papillomavirus genes for therapeutic purposes.

Boursnell *et al.* further contemplate multivalent compositions for treating HPV-induced cervical cancer and provides a method for circumventing recombination event associated with the expression of homologous sequence. To this end, Boursnell *et al.* provide a recombinant expressing early papillomavirus polypeptides encoded by different HPV strains, *i.e.,* the HPV-16 E6, HPV-16 E7, HPF-18 E6 an HPV-18 E7 (*see* the paragraph bridging columns 2 and 3) that are arranged in reverse orientation each other in order to reduce the likelihood of recombination between the homologous sequences of the different HPV strains. Taken as a whole, Applicants submit that both examples and the specification of Boursnell support the fused arrangement between E6 and E7 genes, rather than independent expression. For example, Figure 26 a-g shows a variety of options for arrangement of the papillomavirus genes in the recombinant vector. However, only one option (designed in Figure 26c) refers to a nonfused expression of the HPV-16 and 18 coding sequences, while the six other options recommend a fused arrangement (*see* Figure 26a, b, d, e, f, and g). Taken in its entirety, Boursnell *et al.* promotes the fused arrangement (*see* the paragraph at the bottom of column 5, column 6, and the paragraph at the top of column 7). In fact, Boursnell *et al.* disclose in the paragraph

bridging columns 9 and 10 that "Expression of the desired four gene sequences could also be difficult to achieve as independent expression units, and so the invention provides that instead, the E6 and E7 open reading frames may be fused together."

In contrast to the Examiner's assertion, expression of multiple genes from different promoters in a single vaccinia vector can be problematic as recognized in the art. Thus, Applicants submit that the skilled artisan would have no expectation of success in expressing four papillomavirus polypeptides in a single vector under independent regulatory elements.

Galloway et al.

Galloway *et al.* disclose that early papillomavirus polypeptides can be used for therapeutic purposes or the late papillomavirus polypeptides for prophylactic purposes (*see* Abstract). Galloway provides review of preclinical studies that have been performed with either late papillomavirus polypeptides recombinantly produced as fusion proteins (*see* page 190, second column) or individual early papillomavirus polypeptide (*see* page 191 from the second sentence to the end of the first paragraph of the first column).

The presently claimed invention is directed to recombinant MVA vector for use in the express of both early E7 and E7 and the late L1 and L2 papillomavirus polypeptides from independent regulatory control elements (*i.e.* in a non-fused manner). As described in the present specification, the method of the invention provides for prophylactic and therapeutic protection against HPV-induced tumors.

These elements of the present invention are not disclosed or even suggested by the cited references. Upon reviewing the cited references, alone or in combination, there is no way of knowing whether independent expression of both early and late papillomavirus genes from a recombinant MVA vector would enable appropriate presentation of the papillomavirus antigens to the host's immune system.

There is also no expectation of success that administration of a MVA vector expressing both early and late papillomavirus polypeptides independently from each other would confer antitumoral activity. In fact, Lowy et al. provides data regarding production of neutralizing antibodies in immunized animals, that is not predictive of success for the recombinant MVA vector used with the method of the present invention to achieve protection against preexisting HPV tumors.

Applicants further emphasize that E6 and E7 polypeptides are nuclear polypeptides. The recombinant MVA vector used in the method of the present invention enables the production of the papillomavirus polypeptides inside host cells. Thus, the papillomavirus antigens are processed such that they are accessible to the immune system. In contrast, Lowy *et al.* disclose the presentation of the E7 polypeptide at the VLP surface to be amenable to the host's immune system.

Applicants further note that the vast majority of HPV-infected patients develop antibodies to the external L1 papillomavirus protein as they become infected (*see* for example Galloway at the bottom of page 189). Therefore, using chimeric VLPs for delivering E7 into an HPV-infected patient is likely to at least reduce the E7-mediated cell immune response due to the risk of neutralization by pre-existing anti-L1 antibodies present in HPV-infected patients.

In addition, the prevalence of antibodies against some HPV proteins is not representative of the disease stated, as further explained in Galloway. Galloway discloses that the adding of several groups had demonstrated that the prevalence of antibodies to the HPV 16 or 18 E7 protein is increased in cases with cervical cancer compared with age-matched controls (*see* page 189, first paragraph, second column). Thus, development of an humoral (antibody-based) immune response in HPV-infected patients as demonstrated by Lowy's chimeric VLPs, may not correlate with a protective antitumoral effect.

Accordingly, as disclosure of the cited references that early polypeptides should be fused to a late (*e.g.* L2) polypeptide to be efficiently presented to the host's immune system, one skilled in the art would not be motivated to rely on non-fused papillomavirus early and late polypeptides.

In summary, the cited references do not disclose a method for treating or preventing HPV-induced lesions using a MVA vector expressing in combination late L1 an L2 and early E6 and E7 antigens, as claimed in the present invention. There is no motivation provided by the cited references, either alone or in combination, to combine late and early papillomavirus genes, or to use a MVA vector expressing multiple and non-fused papillomavirus polypeptides (*i.e.*, 4 papillomavirus genes expressed from independent control elements). In fact, the cited references disclose the insertion of the sequences encoding the early HPV polypeptides into the coding sequence of the late L2 polypeptide to improve accessibility to the host's immune system and that the expression of multiple genes from independent promoters in a single vaccinia vector could be difficult to achieve.

Claim 40 stands rejected under 35 U.S.C. 103(a) as purportedly unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (*Journal of Virology*. 1993; 67 (1): 315-322), Borysiewicz et at. (*Lancet*. June, 1996; 347: 1523-1527), Galloway (*Infectious Agents and Disease*. 1994; 3:187-193), and Meyer et at. (*Journal of General Virology*. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054), and further in view of Crook et at. (*Cell*. 1991; 67: 547-556) and Munger et al. (*EMBO Journal*. 1989; 8: 4099-4105).

Applicants further note that claim 40 is dependent on 32. As discussed above with reference to claim 32, none of the cited reference provide disclosure and/or motivation for the skilled artisan to use a MVA vector composition expressing independently (*i.e.*, non-fused) E6, E7, L1 and L2 papillomavirus polypeptides. Thus, in light of the arguments above, Applicants submit that the references are not applicable to claim 40.

Claims 44, 46, 48, 55, 56, 62 and 64 stand rejected under 35 U.S.C. 103(a) as purportedly unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (*Journal of Virology*. 1993; 67 (1): 315-322), Borysiewicz et al. (*Lancet*. June, 1996; 347: 1523-1527), Galloway (*Infectious Agents and Disease*. 1994; 3:187-193), and Meyer et al. (*Journal of General Virology*. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054), and further in view of Bubenik et al. (*International Journal of Oncology*.1996; 8: 477-481). Applicants respectfully traverse.

Bubenik et al. fail to remedy the deficiencies of the other references, as previously discussed. Bubenik *et al.* disclose a therapeutic strategy which involves

administration of HPV-16 infected tumor cells and repeated injection of recombinant IL-2. The animals vaccinated with irradiated cells plus IL-2 were protected to a greater extent than animals only treated with irradiated cells. The administration protocol described herein requires two administrations of immunizing irradiated cells and twenty injections of recombinant IL-2 before being challenged with tumor cells.

Applicants submit that Bubenik et al. neither disclose or even suggest a method as claimed in the present invention based on the direct administration of a MVA vector expressing a combination of L1, L2, E6 and E7 papillomavirus polypeptides and an immunostimulating polypeptide. Bubenik *et al.* disclose a cellular approach which relies on the administration of an immunogenic composition (*i.e.* irradiated tumor cells) and separate and repeated administrations of IL-2 (20 injections of IL-2). In fact, the Bubenik's method would be very difficult to implement for treating or preventing HPV-induced cancers in human patients compared to the method of the present invention.

Applicants submit that the statement in the Office Action that multiple injections of IL-2 provides another motivation to one skilled in the art for expressing IL-2 in the MVA expression vector is incorrect. The technological teachings of Bubenik *et al.* are limited to the fact that huge quantities of IL-2 as compared to the vaccinating irradiated tumoral cells are required to augment the immune response to HPV-16 infected cells. The assertion in the Office Action that expression of IL-2 from an independent expression cassette would enable the quantity of IL-2 required to induce the adjuvanting effect described by Bubenik does not come from the cited reference itself. In stead, it appears to be speculation in the Office Action.

In fact, there would be no way of knowing how to produce the huge quantities

of IL-2 compared to the papillomavirus components that are necessary to influence the anti-papillomavirus immune response. Expression of papillomavirus polypeptides is placed under the control of effective promoter elements and identifying a promoter element providing 20 times more of cytokine is not predictive of success. Bubenik's approach fails to provide a reasonable expectation of success to one of ordinary skill in the art with respect to the direct administration of a MVA vector expressing L1, L2, E6 and E7 papillomavirus polypeptides and an immunostimulator polypeptide.

Claim 49 stands rejected under *35* U.S.C. 103(a) as being unpatentable over Lowy *et al.* (US 5,618,536), Hagensee *et al.* (*Journal of Virology*. 1993; 67 (1): 315-322), Borysiewicz *et al.* (*Lancet.* June, 1996; 347: *1523-1527),* Galloway (*Infectious Agents and Disease*. 1994; 3:187-193), Meyer *et al.* (*Journal of General Virology.* 1991; 72: 103 1-1038), as further evidenced by Boursnell *et al.* (US 5,719,054*),* and Bubenik *et al.* (*International Journal of Oncology*. 1996; 8:477-481), and further in view of Crook *et al.* (*Cell.* 1991; 67: 547-556*)* and Munger *et al.* (*EMBO Journal.* 1989; 8: 4099-4105).

Claim 49 depends upon claim 48. As discussed above with regard to claim 48, none of the cited references provide disclosure and motivation for the skilled artisan to use a MVA vector composition expressing independently (*i.e.*, non-fused) E6, E7, L1 and L2 papillomavirus polypeptides and IL-2 as claimed in independent claim 48.

Claims 65, 69, 71, 72, 74, 79 and 80 stand rejected under 35 U.S.C. 103(a) as purportedly unpatentable over Borysiewicz et al. (*Lancet.* June, 1996; 347: 1523-1527), Meyer et al. (*Journal of General Virology.* 1991; 72: 1031-1038) and Bubenik *et al.* (*International Journal of Oncology.* 1996; 8: 477-48), as further evidenced by Boursnell et al. (US 5,719,054).

The present claims are directed to a composition and a method for treating or preventing HPV-associated diseases using a recombinant MVA vector expressing E6, E7 and an immunostimulatory polypeptide (*i.e.*, IL-2, IL-7 or B7.2), each under independent control elements.

The Office Action notes that Borysiewicz *et al.* only teach fused papillomavirus polypeptides in the absence of immunostimulator. However, the Office Action states that the skilled person would have motivation to reach the claimed composition on the basis of prior art references disclosing recombinant MVA vectors (Meyer *et al.*), expression of nonfused papillomavirus polypeptides from a vaccinia vector (Boursnell *et al.)* and the adjuvanting effect of IL-2 in combination with irradiated HPV tumor cells (Bubenik).

Meyer is merely a background reference disclosing how to make and use recombinant MVA vectors.

Boursnell *et al.* discloses that expression of multiple genes from independent promoters can be difficult to achieve (*see* column 9, lines 64-67 and column 10, line 1). Bubenik *et al.* disclose a cellular approach (administration of irradiated tumor cells) requiring separate and repeated administrations of IL-2 (20 injections of IL-2) to observe an adjuvanting effect. As discussed above, Bubenik's approach fails to provide a reasonable expectation of success to one of ordinary skill in the art with

respect to the direct administration of a MVA vector expressing independently E6 and E7 papillomavirus polypeptides and IL-2 since there would be no way of knowing how to produce the huge quantities of IL-2 compared to the papillomavirus components that are necessary to influence the anti-papillomavirus immune response, especially in view of the teaching by Boursnell that expression of more than 2 expression units can be difficult to achieve.

Claim 75 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Borysiewicz *et al.* (*Lancet.* June, 1996; 347: 1523-1527), Meyer *et al.* (*Journal of General Virology.* 1991; 72: 1031-1038) and Bubenik *et al.* (*International Journal of Oncology.* 1996; 8:477-48 1) and further evidenced by Boursnell *et al.* (US 5,719,054) and further in view of Crook *et al.* (*Cell.* 1991; 67: 547-556) and Munger *et al.* (*EMBO Journal.* 1989; 8: 4099-4105).

Claim 75 is dependent upon claim 65. As discussed above, none of cited references provide disclosure or motivation for the skilled artisan to use a MVA vector composition expressing independently (*i.e.* non-fused) E6, E7 papillomavirus polypeptides and an immunostimulator polypeptide as claimed in independent claim 65.

In light of the above remarks and amendments, Applicants request that the rejections under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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Date: October 7, 2004

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